Emerging Infections 4
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Chapter 5

Monkeypox: an Emerging Infection for Humans?

Joel G. Breman

Human monkeypox was first identified in 1970 in the Democratic Republic of the Congo (DRC) in an area where smallpox had been eliminated about 2 years previously (53, 57). From 1970 to 1986, 404 cases were reported from tropical rain forest areas in seven western and central African countries (7, 41). Monkeypox, a zoonotic and probably respiratorily acquired disease, resembles smallpox clinically but differs biologically and epidemiologically (23, 25, 41); of all these differences, the most important is that spread between humans is limited. Undoubtedly, the disease had existed previously but was mistaken for smallpox, which was widespread in the DRC and elsewhere in western and central Africa until 1971. While only 14 monkeypox cases were reported from 1987 to 1992 (and none from 1993 to 1995), there have been several outbreaks and over 500 suspected cases reported since 1996 in the central DRC, where war has been occurring (35, 85). Even though most of these cases have not been confirmed by laboratory testing, there is concern that human monkeypox may be making a resurgence (14).

BIOLOGY, PATHOGENESIS, AND LABORATORY DIAGNOSIS

Monkeypox virus, like other orthopoxviruses, contains a single molecule of double-stranded DNA, with inverted terminal repeats. The virus is genetically distinct from variola virus (the cause of smallpox), vaccinia virus (the virus used as a vaccine against smallpox), and other orthopoxviruses (Fig. 1). The DNAs of monkeypox virus derived from captive monkeys and from human patients show only minor differences, and these are ascribed to geographic differences rather than being host related (15–18, 22, 22a, 24, 55, 66, 71). Virions of monkeypox are about 250 nm by 200 nm and contain distinctive polypeptides located in the outer part of the virion.

Joel G. Breman • Division of International Training and Research, Fogarty International Center, National Institutes of Health, Bethesda, MD 20892-2220.

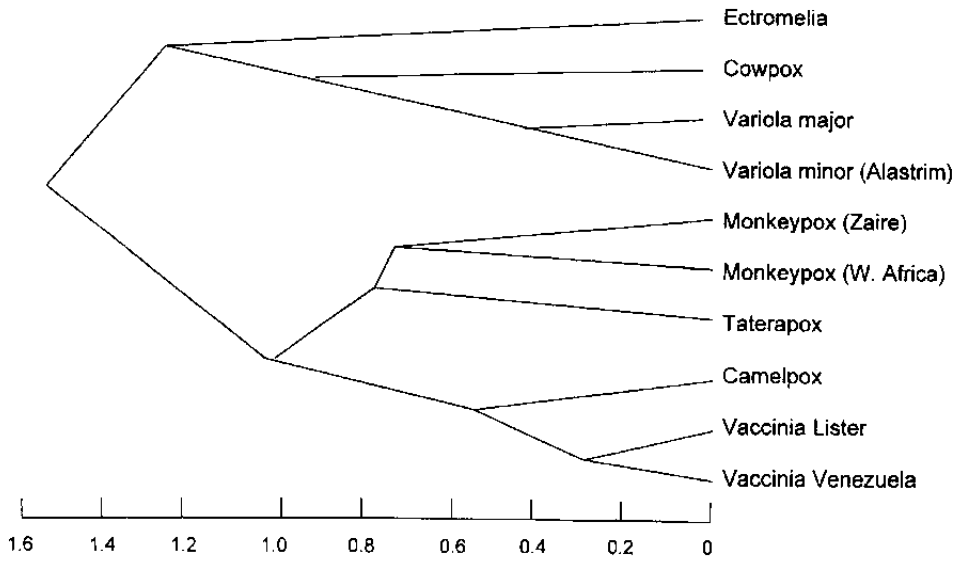

Figure 1. Dendrogram illustrating the similarities and differences between orthopoxvirus DNAs. Modified from reference 23.

Experimental monkeypox infections in several species of animals, including nonhuman primates, have demonstrated infectivity and pathogenesis following infection by aerosol, intranasal inoculations, or parenteral administration (3, 13, 25a, 32, 33, 41, 60, 80, 81). The sequence of events is similar to that of other orthopoxviruses.

During the first week of infection, there is regional lymph node uptake and replication of virus in lymphoid organs, followed by viremia from day 3 to 14. An eruption begins the second week, with lesions evolving successively from macules, papules, vesicles, pustules, and crusts to scarring from days 8 to 23 of infection. Foci of inflammation and cell necrosis have been seen in tonsils, lymph nodes, digestive tract, testes, ovaries, kidneys, liver, and lungs. Epithelial degeneration, necrosis, and intracytoplasmic bodies have been seen in skin and mucous membranes.

Major biologic features of monkeypox virus that distinguish it from other orthopoxviruses are small, opaque, and hemorrhagic pocks on chorioallantoic membranes of chicken eggs; a ceiling growth temperature of 39°C; indurated hemorrhagic lesions on rabbit skin; a generalized rash in monkeys; and high lethality for mice and medium lethality for chick embryos (13, 24, 41). Monkeypox cross-reacts antigenically and serologically with other orthopoxviruses (20, 21, 24). Cross-absorption and gel precipitation tests allowed monkeypox to be differentiated from vaccinia and variola viruses under various conditions, but these have not become standard assays (30, 31, 37, 70, 78, 79, 86).

A major challenge for unraveling the epidemiology and ecology of monkeypox virus has been the development of a sensitive, specific, and predictive serologic

test. The radioimmunoassay adsorption was promising but has not been used in recent years because of technical difficulties in dealing with animal sera, particularly the requirement for the use of labeled antibody to the gamma globulin of the animal species from which the serum under tests was obtained (72). A radioactive iodine-labeled staphylococcal protein A was found to bind to the gamma globulin of several species of African wild animal and was used for testing sera from African animals. More recently, PCR and monoclonal antibody technology have offered promise for more sensitive and specific diagnosis (38, 62, 67, 73).

In the 1970s, it was claimed but never confirmed that variola virus might be readily derived from monkeypox virus (19, 23, 29, 56, 58, 68). More recently, a sequence in monkeypox virus DNA with multiple deletions has been identified, providing stronger evidence that monkeypox virus is not ancestral to variola virus (15, 16). This and other evidence strengthen confidence in the long-term success of smallpox eradication.

OUTBREAKS IN MONKEYS AND NATURAL HISTORY

Monkeypox is so named because nine outbreaks in nonhuman primate colonies in laboratories and a zoo occurred between 1958 and 1968 (Table 1) (1, 2, 13, 41, 69, 77). Monkeypox virus was recovered from animals in six of the outbreaks, and no humans were infected (1, 2, 41). Six of the outbreaks of monkeypox occurred only in Asian monkeys. In the other outbreaks a mixture of animals from Asia and Africa, and Asia, Africa, and South America was reported; in one episode, an African chimpanzee was affected. While primates from Asia, Africa, and South America were infected with monkeypox virus in captivity, there is no serologic, virologic, or epidemiologic evidence that the virus occurs naturally anywhere except Africa (2). During the 1950s and 1960s, large numbers of primates were imported into North America and Europe from Asia and, to a lesser extent, from Africa, mainly for the production and testing of polio vaccine. During these transfers, there were many contacts of nonhuman primates with other wild animals and chances of contracting infections from them. In one episode in Amsterdam, The Netherlands, two South American giant anteaters developed a vesiculopustular disease (presumed to be monkeypox) in the Blijdorp Zoo, where they had been placed in the monkey house without being quarantined; they infected an orangutan, and the disease spread throughout the monkey colony (41, 69). Monkeypox outbreaks in captive animals stopped in the late 1960s following improvements in animal shipping standards and increased use of animals bred in captivity.

The clinical features of monkeypox vary among the different primate species. The disease is particularly severe in orangutans and mild in rhesus monkeys and in three species from Africa—green monkeys, baboons, and chimpanzees. The incubation period is between 3 and 10 days in animals experimentally infected by the parenteral route and 10 days in animals naturally infected by the respiratory route (13, 33, 41, 60, 69, 77, 80). The disease begins with sudden onset of fever 3 days after inoculation, with concomitant cough, coryza, listlessness, and decreased appetite. Generalized lymphadenopathy develops in the first week of infection and remains for 3 weeks of illness. The eruption begins 7 to 11 days after

Table 1. Monkeypox in captive animals, 1958 to 1968

Country	Yr	Infected species	Origin of index animal	Time to illness after arrival	Virus isolated[a]
Denmark	1958	Cynomolgus (*Macaca irus*) monkeys	Singapore	51–62 days	Yes
USA	1959	Cynomolgus, rhesus (*Macaca mulatta*), and African green (*Cercopithecus aethiops*) monkeys	Malaysia	Recently arrived	Yes
USA	1962	Cynomolgus and rhesus monkeys	?	9 months	Yes
Holland	1964	Giant anteater (*Myrmecophaga tridactyla*) (index), orangutan (*Pongo pygmaeus*), gorilla (*Gorilla gorilla*), chimpanzee (*Pan troglodytes*), gibbon (*Hylobates lar*), squirrel monkey (*Saimiri sciureus*), cercopithecus, marmoset (*Callithrix jacchus*)	Unknown, from dealer in zoo animals	?	Yes
USA	1965	Cynomolgus monkey	Malaysia, Philippines	?	No
USA	Before 1966	Rhesus monkey	India	?	No
USA	1966	Rhesus monkeys	India	Recently arrived	No
USA	1966–1967	Indian and Malayan langurs (*Presbytis entellus*); rhesus, cynomolgus, and pigtailed macaques	India, Malaysia	2 years	Yes
France	1968	Chimpanzee	Sierra Leone	11 days	Yes

[a]Serologic confirmation was done when no virus was isolated.

infection, with maculopapular lesions, varying from 2 to 5 mm in diameter. These lesions are dispersed over the body, with increased numbers on the palms and soles. Lesions on the lips, eyelids, scrotum in males, and oral and pharyngeal mucosa are also seen. Lesions progress through papules, vesicles, and pustules over about 1 week before crusting begins; crusting lasts for 2 to 3 days before the crusts fall and leave small scars. The case fatality rate varied from <3 to 40% among orangutans. A fatal prognosis was associated with severe rash, dehydration, decreased weight, hypothermia, and vascular collapse.

Inapparent infections undoubtedly occurred in outbreaks among captive animals. Antibodies to orthopoxviruses often developed in these exposed animals in the absence of signs, and monkeypox virus was recovered from the kidneys of some healthy-appearing animals, probably having subclinical infections (41). Serological studies of a wide variety of nonhuman primates and other animals (rodents, larger mammals, and birds) captured in the wild in Africa, without evidence of illness, showed that a substantial percentage had orthopox antibodies (5–7, 23, 41, 47).

While it has been presumed that these were monkeypox antibodies, it is possible that other animal orthopoxviruses are circulating in Africa. The only isolation of monkeypox virus from an animal found in nature occurred in DRC in 1986 in an animal collected near a monkeypox case (41, 50–52, 59). A "sick" squirrel (*Funisciurus anerythrus*), common in agricultural fields near villages, was found with several skin lesions, 2 to 3 mm in diameter. Organ specimens from the animal were collected and divided in the field, and monkeypox virus was isolated from two World Health Organization (WHO) Collaborating Centers, in Atlanta, Ga., and Moscow, Russia. Despite subsequent large-scale virologic testing of animals collected in DRC, monkeypox virus has not been found subsequently. It is assumed that monkeypox is a zoonosis and that periodic epizootics may be occurring. It is also assumed that direct animal-to-human contact is needed for transmission. This occurs often during frequent trapping, hunting, and preparing wild game for cooking and during the close contact that rural villagers have with animals in and near their homes (52). In one instance, a chimpanzee had close contact with a young child who later contracted monkeypox (65). While squirrels may be the reservoir host, they may have contact with other animals and their excreta in the wild; the natural history of human monkeypox remains obscure.

CLINICAL PRESENTATION OF HUMAN MONKEYPOX AND DIFFERENTIAL DIAGNOSIS

Following an incubation period of 7 to 17 days (mean, 12 days), a prodrome of fever, headache, backache, and fatigue begin. The cutaneous eruption caused by monkeypox in humans resembles that in monkeys and includes macules, papules, vesicles, pustules, and crusts; lesions evolve in the same stage over 14 to 21 days, similar to smallpox, with crusting occurring over the last week of illness (Fig. 2). Hypopigmentation, and later hyperpigmentation, of lesions remains in over 50% of patients for 2 years or longer. The major differences between smallpox and monkeypox are pronounced postauricular, submanidibular, cervical, and inguinal lymphadenopathy in a large majority of patients with monkeypox that are not noted

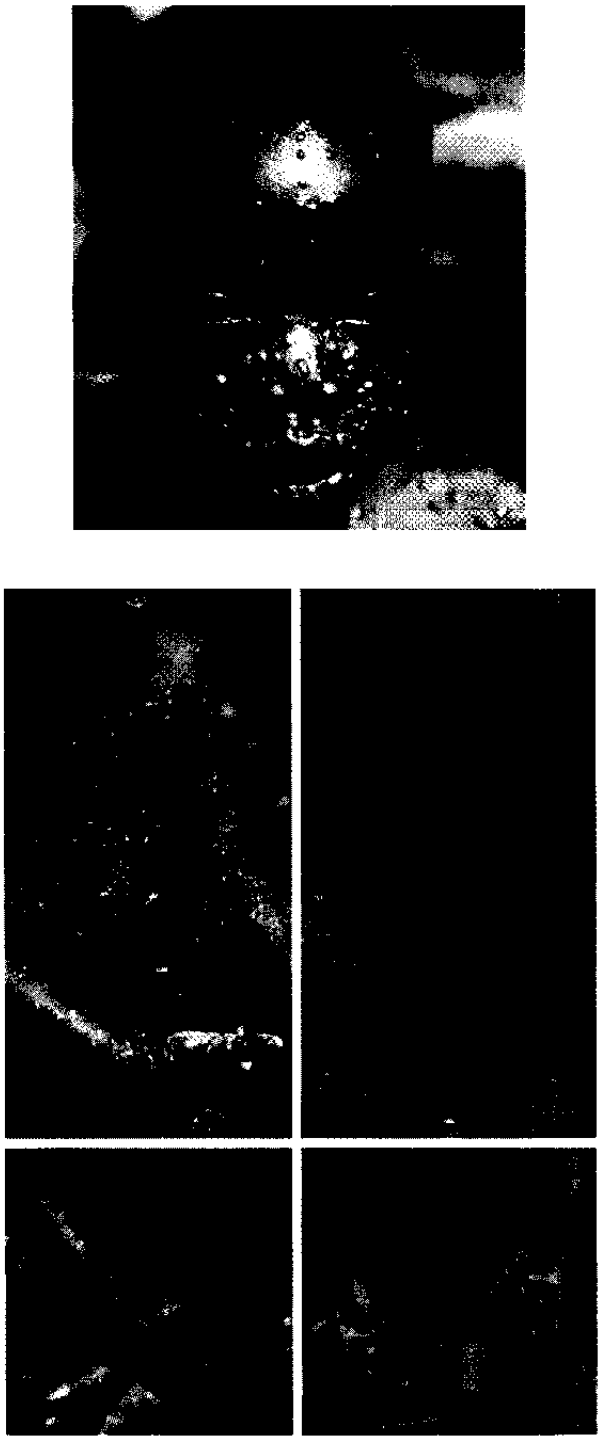

Figure 2. Five photos of a child with monkeypox on the 8th day of rash. Note inguinal lymphadenopathy and dense concentration of lesions on the lower face and hands. (Photos courtesy of World Health Organization, M. Szczeniowski.)

with smallpox; the occurrence of monkeypox cases in small forest villages in western and central Africa, whereas smallpox was cosmopolitan; through the 1980s, the predominance of children with monkeypox (median age, 4 years), whereas smallpox would affect unvaccinated persons of all age groups (this is changing as the entire at-risk population becomes susceptible to orthopoxviruses following the cessation of smallpox vaccination); relatively inefficient interhuman transmission of monkeypox (the secondary attack rate in susceptible family contacts is about 10% or less, compared with 37 to 88% for smallpox) (23); and interhuman spread to a fourth generation is rare with monkeypox (smallpox was spread by continuous person-to-person transmission). The case fatality rate for monkeypox has been about 10 to 16%, the same rate as seen previously with smallpox in western and central Africa (7, 23, 41, 48). Vaccination with vaccinia virus has provided >85% protection against monkeypox (7, 23, 41).

Numerous infections and other syndromes that cause papulovesicular and vesiculopustular eruptions can resemble human monkeypox (Table 2). The most common and difficult diagnostic challenge is to distinguish monkeypox from atypical or severe chickenpox, particularly in rural areas of Africa where chickenpox may not have been evident for several years (8, 76). Chickenpox has a shorter and milder prodrome and clinical course, lymphadenopathy is not prominent, and death is uncommon (8, 49). Lesions are smaller, more superficial, concentrated more on the trunk (centripetal rather than centrifugal), and evolve in different stages ("crops") over 3 to 5 days. Immunosuppressed persons and adults may have very severe chickenpox with an increased case fatality rate. Manifestations of other poxviruses, some of which have similar individual lesions, may cause diagnostic confusion and are listed in Table 3. Except for variola virus, the others cause few lesions and are usually localized to the skin area where the inoculation occurred by direct contact. Tanapox is endemic in the DRC and other African countries and causes few individual lesions, but these can remain for weeks or months (40). Atypical eruptions, such as those caused by allergic reactions to drugs and insect bites, can resemble monkeypox and chickenpox, particularly for clinicians unfamiliar with these diseases.

EPIDEMIOLOGY, 1970 TO 1986

Between 1970 and 1979, the first investigations of human monkeypox occurred in tropical rainforest areas of several western and central African countries during concurrent smallpox eradication (and certification of eradication) activities. During this period, 54 cases of human monkeypox were confirmed in forested areas of western and central Africa, of which 44 (80%) were recorded in the DRC (5, 6, 27, 41, 53, 54, 57). Human-to-human transmission of monkeypox was infrequent, possibly occurring in only five instances (6). Spread of the disease to a third generation was not observed during the first 10 years of monkeypox field studies. It was noted that the population at risk had moderately high levels of immunity after vaccination with vaccinia virus, up to 80% or more in several investigations, which is as protective against monkeypox as it is against smallpox. These and later find-

Table 2. Causes of papulovesicular and maculopapular eruptions

Papulovesicular eruptions	Maculopapular eruptions
Atypical measles (rubeola)	AIDS (HIV)
Chickenpox (varicella)	Adenoviruses
Coxsackie virus infections (hand, foot and mouth disease, A-16)	Arboviruses (dengue, chikungunya, o'nyong-nyong)
Dermatitis herpetiformis	Atypical measles (rubeola)
Drug eruptions	Cytomegalovirus infection
Eczema herpeticum (herpes simplex virus)	Drug eruptions
Generalized vaccinia and eczema vaccinatum (vaccinia)	Epstein-Barr virus
Impetigo	Enteroviral infections (echovirus 1–7, 9, 11, 12, 14, 16, 18–20, 25, 30; coxsackieviruses A4, A6, A10, A16, B2, B3, B5)
Insect bites	Erythema infectiosum (parvovirus B19)
Molluscum contagiosum	Exanthem infectiosum (herpesvirus type 6)
Monkeypox	German measles (rubella)
Papular urticaria	Infectious mononucleosis
Rickettsialpox (*Rickettsia akari*)	Measles (rubeola)
Shingles (varicella-zoster virus)	Meningococcemia
Yaws (*Treponema pallidum* subsp. *pertenue*)	Mucocutaneus lymph node syndrome (Kawasaki disease)
Smallpox, eradicated (variola)	*Mycoplasma pneumoniae*
	Roseola infantum
	Scalded skin syndrome (*Staphylococcus aureus*)
	Scarlet fever (*Streptococcus pyogenes*)
	Sunburn
	Syphilis, secondary (*Treponema pallidum* subsp. *pallidum*)
	Rat bite fever (*Streptobacillus moniliformis*)
	Reoviruses
	Rocky Mountain spotted fever (*R. rickettsii*)
	Toxic erythemas
	Toxic shock syndome (*Staphylococcus aureus*, phage group I)
	Toxoplasmosis
	Typhus and tick fevers (*R. prowazekii, R. typhi, Coxiella burnetii*)
	Typhoid (*Salmonella enterica* serovar Typhi)
	Vaccine reactions (live virus)

ings are described in detail in a comprehensive monograph on monkeypox by Ježek and Fenner (41).

In 1980, with smallpox eradication completed and confirmed worldwide, surveillance for monkeypox was further strengthened in the DRC with support from WHO and included a widely publicized monetary reward to encourage reporting. From 1980 to 1986, an additional 350 cases were detected, 342 (98%) of them in forested areas of DRC. Between 1970 and 1986, human monkeypox cases were also reported in the forests of Cameroon (1 case), Central African Republic (6 cases), Côte d'Ivoire (2 cases), Liberia (4 cases), Nigeria (3 cases), and Sierra

Table 3. Clinical manifestations of human diseases caused by poxviruses

Genus and species	Manifestations	Zoonosis
Orthopoxviruses		
Cowpox virus	Localized pustular skin lesions	Rare
Monkeypox virus	Systemic illness with generalized skin lesions in same stage of evolution; peripheral distribution (smallpox-like) and lymphadenopathy	Rare
Vaccinia virus	Localized "Jennerien vesicle" on skin for primary vaccination and nodule for revaccination; complications include postvaccinal encephalitis, eczema vaccinatum, progressive vaccinia, generalized vaccinia, and ocular vaccinia	No
Buffalopox virus (vaccinia virus of buffalo)	Localized pustular skin lesions; affects milkers in India	Rare
Variola virus (eradicated)	Systemic illness with generalized skin lesions in same stage of evolution and peripheral distribution	No
Parapoxviruses		
Bovine papular stomatitis virus	Localized nodular skin lesions	Rare
Orf virus	Localized nodular skin lesions	Rare
Pseudocowpox	Localized nodular skin lesions	Rare
Yatapoxviruses		
Tanapox virus	Localized nodular skin lesions	Rare
Yabapox virus	Localized nodular skin lesions	Rare
Molluscipoxvirus		
Molluscum contagiosum virus	Multiple thick-walled pustular skin lesions	No

Leone (1 case) (Table 4). Essentially all of the episodes occurring outside the DRC were single events with no evidence of secondary spread.

How readily does monkeypox spread between humans? Of 338 patients studied in depth in DRC between 1981 and 1986, 245 (72%) were primary or coprimary (probably infected at or about the same time as the primary) cases, presumably infected from an animal or animal tissue (39, 41, 43–46, 65). About 52% of the cases were between 0 and 4 years of age and 37% were between 5 and 9 years of age, reflecting, in general, the most vulnerable population; 96% of these children had never been vaccinated against smallpox. Only 69, 19, 4, and 1 patient represented assumed spread to a second, third, fourth, and fifth generation of patients, respectively. Thus, a total of 93 cases (28%) resulted from possible person-to-person transmission; of these, 74% spread to only one subsequent generation and no further.

Field investigators identified 723 unvaccinated contacts of the 338 cases, of which 431 (60%) were household contacts of the primary or coprimary cases. Only 40 of these unvaccinated contacts developed disease, a secondary attack rate of 9.3%. This is substantially less than the rates of 37 to 88% which were seen with smallpox or even higher with measles, chickenpox, and influenza (23, 36).

Table 4. Human monkeypox patients reported from western and central Africa, 1970–1999

Country	No. of cases reported			
	1970–1986	1987–1995	1996–1999	Total
Cameroon	2	4		6
Central African Republic	6			6
Côte d'Ivoire	2			2
DRC[a]	386	2	511?	899?
Gabon		8		8
Liberia	4			4
Nigeria	3			3
Sierra Leone	1			1
Total	404	14	511?	929?

[a]Only a small number of the cases reported in the DRC from 1996 to 1999 were confirmed by laboratory tests; chickenpox was circulating concurrently in monkeypox-affected communities. The DRC was known as Zaire from 1971 to 1997.

Knowing that cessation of vaccination would render the overall population more susceptible, computer simulations were performed in the 1980s to determine the probability of persistence of transmission using data acquired during active surveillance in Zaire between 1980 and 1984 (26, 42). The model generated chains of transmission such as might arise by chance from individual primary and coprimary cases. Simulations which reduced vaccination coverage to zero predicted that 147 introductions (as was observed during the study period) could generate 182 to 355 (average, 257) additional cases due to person-to-person infection, with individual outbreaks lasting as long as 11 generations. A "worst-case" scenario was modeled, assuming an observed secondary attack rate of 13.5% for household contacts and 4.7% for non-household contacts, representing the upper 95% confidence limits of the observed attack rates. With this simulation, the 147 primary cases would give rise to 290 to 661 secondary cases (average, 424), with the possibility that individual outbreaks might last up to 14 generations before dying out. It was concluded that continued transmission of monkeypox indefinitely was unlikely, but expert groups advised the WHO that the situation continue to be monitored (23, 41).

SURVEILLANCE AND EPIDEMIOLOGY, 1987 TO 1999

Since 1987, WHO and countries where monkeypox is endemic continued monkeypox surveillance activities in western and central Africa but at greatly reduced levels due to other priorities. Laboratory confirmation of specimens continued at the WHO Collaborating Centers for Orthopoxvirus Infections at the Centers for Disease Control and Prevention, Atlanta, and the Institute for Viral Preparations in Moscow, both WHO collaborating centers. Patients with monkeypox were confirmed in 1987 (three in Gabon and one in the DRC), 1990 (four in Cameroon), 1991 (five in Gabon), and 1992 (one probable case in the DRC) (35, 61, 64, 82). There were no reports of monkeypox outbreaks between 1993 and 1995, probably due to inadequate surviellance.

In 1996, staff from the Katoko-Kombé health zone, Sankuro subregion, Kasai Oriental Province, central DRC, reported many patients with human monkeypox in 13 villages. Three WHO-sponsored, short-term missions were undertaken to investigate this outbreak and continuing reported cases through July 1998 (11, 12, 35, 63, 83–85). From February through August 1996, 71 persons were alleged to have acquired human monkeypox, of whom 6 (8%) died. An investigation in July 1996 determined that 42 of the cases, including 3 (7%) deaths, had occurred in one village of 346 persons. This extremely high attack rate in one village (12%) was without precedent. Most patients were under 25 years of age and unvaccinated; the DRC, like other countries, had stopped routine vaccination against smallpox in the early 1980s, as advised by WHO after certification of eradication (23, 91). Monkeypox virus was confirmed in 11 clinically suspect patients by several laboratory analyses, including (for three scab samples) virus-specific PCR amplifications of genes for the monkeypox virus hemagglutinin and tumor necrosis factor receptor (62, 63). In the sera of 10 patients, orthopoxvirus genus-specific immunoglobulin G (IgG) was shown by Western blot assay. It was speculated that one patient was the source of eight other cases and that secondary spread was "more extensive . . . than previously recognized." Partial sequence analysis of two isolates from the Katoko-Kombé outbreak indicated that Zairian monkeypox strains had not diverged greatly from the first 1970 isolate (63).

In February 1997, another investigative team, restricted in time and movement by military and civil disorder, visited 12 villages in Katoko-Kombé (population, 4,057) and identified 92 additional possible cases that had occurred since January 1996, an attack rate of 2%. Seven patients had active papulovesicular rashes. A total of 15 (18%) of 84 patients had evidence of a possible smallpox vaccination scar, and 65 (73%) of 89 patients reported contact with another patient 7 to 21 days before onset of illness. These 65 patients were considered possible secondary cases, although the history of contact with chickenpox patients, squirrels, and other animals or their tissues in the 3-week period prior to disease onset is unknown. Laboratory specimens were not collected, and confirmation of the diagnosis was not possible for the vast majority of these cases.

Serological confirmation of retrospectively isolated cases proved problematic: orthopoxvirus antibodies were detected by plaque reduction neutralization tests in 41 (54%) of 76 healed patients who provided serum, in 73% by Western blot assay, and in 73% by hemagglutination inhibition. As only 14 (17%) of 84 suspected patients had a smallpox vaccination scar, these findings did not appear to be due to cross-reactivity with vaccinia virus. There was evidence to suggest cocirculation of varicella-zoster virus, as five of six active monkeypox cases living in one household also had serological evidence (IgM) of recent varicella-zoster virus infection. Furthermore, 57 (75%) of 76 sera were seropositive for IgG against varicella-zoster virus. Control sera from unaffected populations were not collected during the early investigations. Hence, from retrospective reports and serological testing, it became exceedingly difficult to determine whether chickenpox, monkeypox, or both were being described by the population or local health staff.

Civil unrest necessitated the premature evacuation of the investigation team from the field in February 1997. However, continuing reports of large numbers of cases were received over the following months.

In August 1997, reports from DRC health workers to WHO indicated that, from March to May 1997, the epidemic was increasing; 170 suspected monkeypox cases and no deaths were reported in the Katoko-Kombé health zone, Sankuro subregion, Kasai Oriental Region: 58 in March, 52 in April, and 60 in May.

An international team organized by WHO investigated a wider area in the epidemic zone in October 1997 (83). During this mission, the case definition was changed to include possible chickenpox cases. An additional 419 cases (total, 511 cases) of human monkeypox were identified as having occurred between February 1996 and October 1997 in two subregions of the DRC; 54 villages in the Katoko-Kombé and 24 villages in the Lodje health zones were visited (0.55 million persons in these zones). The team observed 19 patients with active disease. Monkeypox virus and varicella-zoster virus were identified in nine and four patients, respectively.

Of the 20 active cases from both the February and October 1997 investigations for whom virological confirmation was made, monkeypox virus was detected in 13 patients, varicella-zoster virus in 5 patients, and dual infection in 2 patients. Combining serology results from both studies, approximately 255 (73%) of 350 sera were positive for orthopoxvirus antibodies by at least one test and about 50% were positive by at least three tests. Of the patients with orthopoxvirus antibodies, approximately 70% also had immunoglobulin G (IgG) antibodies to varicella-zoster virus. Human immunodeficiency virus (HIV) confection did not seem to be a significant cofactor; only three of the case sera tested showed HIV antibodies, of which two also had orthopoxvirus antibodies. The overall case fatality rate for the February and October 1997 investigations was about 1%. The analysis suggests that monkeypox infection may have been responsible for a substantial percentage of the 511 patients reporting rash illness onset between February 1996 and October 1997, but how much remains unclear.

In July 1998, another follow-up team visited the area to attempt to collect control sera not obtained during the October 1997 investigation. Monkeypox transmission was continuing, and five active cases were detected and verified virologically (J. Huggins, personal communication, 1999). Local surveillance workers reported several hundred new, suspect cases in the 9 months since the previous mission. Of the 150 control sera collected 9 months after the case sera, 11% were positive for orthopoxvirus antibodies and 33% were positive for varicella-zoster virus IgG (83).

In addition to involving a mixture of confirmed chickenpox and monkeypox cases, there are other differences between the recent outbreak of monkeypox and those reported in the 1970s and 1980s. Of greatest concern is that 22% of the cases were identified initially as primary and the remainder as secondary cases. Relatively mild clinical illness was reported from the recent outbreak; 69% of the patients had <100 skin lesions, 59% had an illness lasting less than 1 week, and only five patients (about 1%) died. Indeed, many of these features are more compatible with chickenpox than monkeypox.

SURVEILLANCE, CONTROL, AND PREVENTION

The apparent increase in monkeypox cases, with spread to adjacent subregions and possible secondary spread, has triggered concern that human monkeypox has

changed and that the new agent is a serious medical threat (14). It will be important to quantitate, by serologic and virologic confirmation, the extent of chickenpox and other papulovesicular diseases that could mimic monkeypox in the area. It is also necessary to define very carefully whether patients with confirmed monkeypox acquired their disease from an animal source or from another patient; this may be very difficult, considering the frequent human-animal contact in the tropical rainforest. In January 1999, DRC health authorities again reported that several hundred suspected monkeypox cases were occurring, but as few specimens had been collected, it was unclear what the specific diagnoses were for those patients. As for the previous 2 years, military battles, civil disorder, and internal migration prohibited comprehensive investigations in the area. In addition, the Kasai Oriental province is the major diamond-mining area in the DRC, and security issues linked to mining accentuate an already difficult and complicated situation.

To get necessary answers on whether there have been changes in the frequency, spread, or geographic distribution of human monkeypox, accurate, complete ascertainment of cases is needed. This will depend on a surveillance system that can detect and report suspected patients promptly, assurance that specimens are collected properly and sent to competent diagnostic laboratories without delay, and guarantee that results of laboratory tests will be sent to WHO, national authorities, field staff, communities, and patients quickly. Current major delays in diagnosis and investigation can be shortened by educating and motivating those living in areas where monkeypox is endemic, including again offering a modest reward for persons reporting a confirmed case. Provision of specimen collection kits and monkeypox technical notes to local medical staff would facilitate diagnosis; the kits could also include information and materials for collection of specimens to diagnose other epidemic diseases (yellow fever, cholera, dysentery, Ebola virus, and Marburg virus disease) as used elsewhere in Africa (53a, 74, 75).

To date, there is no specific treatment for monkeypox. Several antiviral compounds have been evaluated in tissue culture, with comparison of their action against monkeypox, variola, vaccinia, camelpox, and cowpox viruses (9). Three of 23 compounds tested had significant activity against variola virus but only moderate inhibitory activity against the other orthopoxviruses. Cidofovir, its cyclic derivative, and ribavirin are in advanced clinical testing in rodents and the macaque monkey model or have been approved for other viral infections (4).

Supportive medical care, including attention to hydration, antibiotics for skin and respiratory bacterial infections, and nutrition, will prevent complications and death and gain credibility and community cooperation for the local medical staff. Isolation of patients in their villages or local health facility until the crusts have fallen and contact with a minimum number of caregivers will decrease the already low chance of transmission. Persons who have been vaccinated against smallpox, even in the distant past, should be designated as caregivers.

Vaccination with vaccinia virus, while effective against monkeypox, is not indicated for widespread use in areas where monkeypox is endemic, because of the low frequency and transmissibility of the disease, even in areas of endemicity, and the possible complications of vaccinia virus vaccination (10). In addition, HIV and AIDS are highly endemic in the DRC and other countries where monkeypox is

endemic. Immunosuppressed persons are at increased risk of severe complications from vaccinia virus vaccination.

FUTURE PERSPECTIVES ON SURVEILLANCE AND RESEARCH

In January 1999, the Technical Advisory Group Meeting on Human Monkeypox was convened by WHO. The advisory group reviewed the clinical, epidemiologic, and laboratory results from the recent outbreaks and identified areas for further surveillance and research on the public health impact of human monkeypox (85).

The advisory group concluded that there has been an increased incidence of monkeypox infection from 1996 to 1999 compared to the 1970s and 1980s, but how much of an increase remains unclear. Undoubtedly, the increased incidence in the human population is due to declining population immunity, since smallpox vaccination stopped in the DRC in 1982. However, there is no evidence of increased transmissibility. While the number of secondary cases is of concern, this is related to the relatively unprotected state of the population. The household secondary attack rate is similar to historical findings and the partial virus DNA sequence evidence indicates that the current monkeypox viruses are unchanged from earlier isolates. HIV infection is not a significant risk factor, in that the prevalence of HIV and AIDS in the area appears to be low. Although in some respects the clinical features are unchanged from the prior period of intensive surveillance, the current case fatality rates are markedly lower, about 1% compared to >10% between 1981 and 1986. As no ecologic studies were performed recently in the area, it is unclear if an epizootic of monkeypox virus was occurring in reservoir species in contact with humans.

Despite the increased incidence of monkeypox, the situation does not warrant the reintroduction of a smallpox vaccination program, due partially to concerns about adverse events in a population with a potentially increasing HIV seroprevalance.

The surveillance and investigation activities provided valuable insights into human monkeypox in central DRC despite limitations caused by military and civil unrest, poor infrastructure and support, use of different methodologies during the investigations, cocirculation of chickenpox, and reliance on currently available serologic tests, which are not adequately sensitive and specific. Additional laboratory-based, epidemiological, and ecological prospective studies are imperative to understand better the natural cycle of the virus and the true extent of the outbreak. Conclusions and recommendations from the meeting addressed surveillance; control and prevention; information, health education and training; and laboratory and other research issues and follow below (85).

THE FUTURE OF MONKEYPOX RESEARCH: CONCLUSIONS

Epidemiological Surveillance

- The surveillance system for monkeypox is inadequate in the DRC and elsewhere in Africa where human monkeypox may occur.

- There has been variability in investigation methodologies, and the protocols in the WHO Human Monkeypox Surveillance and Investigation Manual have not been used in the field consistently.
- Data are incomplete on transmissibility because the suspected patient investigations have been delayed and control patients have not been studied concurrently.
- Mathematical models developed from 1981 to 1986 indicated that human monkeypox could be transmitted for a maximum of 14 interhuman generations in a totally unvaccinated population under certain field conditions. Mathematical modeling of monkeypox transmission dynamics has not been performed recently.
- Due to delays in investigation, serological confirmation of suspected patients is being performed much more often than virological confirmation. The sensitivity, specificity, and predictive values of the standard orthopoxvirus serological tests and the newer tests are not clearly defined.
- Monkeypox is a zoonosis, yet the reservoir(s) of human monkeypox remains uncertain despite the isolation of monkeypox virus from one squirrel found in the wild. Orthopoxvirus antibodies have been detected in several animal species in the area of endemicity.
- Recent, prematurely concluded investigations have not clarified satisfactorily the clinical, epidemiological, or ecological features of the current monkeypox outbreak(s). It is possible that an epizootic is occurring, requiring more prolonged and sustained investigations.
- Major delays in receiving laboratory results and epidemiological analyses from collaborating laboratories have occurred because of administrative problems and the lack of capacity to perform such tests and analyses in the DRC.
- Skilled staff and resources for performing satisfactory surveillance, investigations, and research are lacking in the DRC and other affected countries.

Control and Prevention

- Several promising antiviral drugs under development may offer therapeutic benefit for monkeypox patients. Cidofovir has demonstrated protection in challenge studies performed in animal models.
- Known complications from smallpox vaccination (vaccinia virus), which protects against monkeypox, and the possibility of an increase in prevalence of HIV and AIDS in areas where monkeypox is endemic are contraindications to smallpox vaccination at this time.

Information, Health Education, and Training

- Health information for the local populations in areas where monkeypox is endemic and training for medical and paramedical staff are needed.

Laboratory Issues

- Laboratory diagnostic and research capabilities for monkeypox are weak in the DRC and elsewhere in areas where monkeypox is endemic.
- With decreased interest in orthopoxvirus research in the past 20 years, capacity for diagnosis and research has declined greatly. Support for strengthening this capacity is needed within the WHO orthopoxvirus collaborating centers and allied laboratories. Reliable tests are needed for serological differentiation of orthopoxviruses, and research into the molecular virology and pathogenesis of monkeypox is required.
- In-country screening and analysis of epidemiological information and samples for laboratory testing could ease the burden on collaborating centers and save resources currently expended on specimen transport.
- The WHO specimen collection and shipment instructions need updating. The field samples coming to WHO-affiliated laboratories are often poorly identified and packaged.

Derived from the above, specific recommendations were made by the advisory group.

THE FUTURE OF MONKEYPOX RESEARCH: RECOMMENDATIONS

Epidemiological Surveillance

1. The reestablishment and strengthening of human monkeypox surveillance systems should detect suspected cases promptly, ensure rapid notification to national and WHO authorities, and elicity timely and comprehensive investigations. While the focus should be in forested areas of Kasai Oriental Province of the DRC, surveillance in other areas of the DRC and other African countries should also be reestablished or strengthened through WHO.
2. An updating of the WHO Human Monkeypox Surveillance and Investigation Manual should be prepared promptly by experts in human monkeypox and diseases resembling monkeypox. A review panel should give special attention to case definitions for routine surveillance, investigations, and re-

search. Case definitions should consider clinical and laboratory criteria.

3. The transmissibility of human monkeypox urgently needs to be determined.
4. Monkeypox mathematical modeling, begun in the 1980s, should be reexplored using current techniques.
5. The sensitivity, specificity, and predictive values of new orthopoxvirus serological assays need to be evaluated as part of prospective investigations; it would be desirable to use sera archived in past monkeypox studies (1970s to 1980s), when virologic confirmation of cases was done. Clinical and epidemiological information should be correlated with virologic and serologic data.
6. Differentiation of monkeypox from other orthopoxviruses by serological testing merits the highest priority.
7. HIV seroprevalence in rural and urban areas within the areas under surveillance and study needs to be determined. In particular, the occurrence and clinical picture of chickenpox and monkeypox in HIV-infected and uninfected patients, particularly children, needs to be studied.
8. Ecological and natural history studies of human monkeypox need review by an expert panel convened to develop a protocol and advise on the feasibility of such studies.
9. A population-based study is advised as the best way to understand the clinical, epidemiologic, and ecologic characteristics of human monkeypox and associated laboratory testing issues. At a minimum, a well-defined population in Kasai Oriental Province with a high level of endemicity should be designated for special-emphasis surveillance.
10. National capability for serologic, and eventually virologic, diagnosis should be evaluated, established, and maintained.
11. Increased resources, training, administrative, and logistical support will be needed to ensure that a satisfactory surveillance system and diagnostic capacity are reestablished.

Control and Prevention

1. Antiviral therapy and research
   - Laboratory screening for antiviral drugs against monkeypox and other orthopoxviruses should be expanded.
   - A preclinical trial and, where appropriate, a clinical trial in the field of cidofovir, the first promising antiorthopoxviral drug, was endorsed with several cautions: attention to feasibility, monitoring of drug side effects, clearance by institutional review boards in collaborating countries, and active

collaboration of scientists in the countries where monkeypox is endemic must occur.

2. Vaccination
   - Currently available smallpox vaccines should not be used in areas where monkeypox is endemic until the epidemiologic picture of monkeypox and the risks from vaccination are clarified.
   - Determination of HIV status of patients and their families and communities is needed to asses the risk of using vaccinia virus vaccines in areas where monkeypox is endemic with a substantial prevalence and incidence of HIV and AIDS.
   - Evaluation of the possible usefulness of attenuated vaccinia virus strains for persons who are immune deficient or otherwise have contraindications to smallpox vaccination is advised.
3. Information, health education, and training
   - Health education for local populations should focus on rapid recognition and reporting to an informed health official.
   - Local health care providers and regional authorities should receive information on differential diagnosis, specimen collection, case management, notification and investigation procedures, and collection and shipment materials.
   - Scientific articles on the previous investigations and technical notes, for the medical care and scientific communities, should be published and distributed widely, particularly in countries where monkeypox is endemic.
   - Increased training is needed for national and local staff in clinical, epidemiologic and laboratory features of monkeypox, and its control and prevention.

Laboratory Issues

1. A central laboratory in highly affected countries (presently the DRC), capable of implementing orthopoxvirus and monkeypox modern diagnostic assays for lesion material (PCR and antigen capture) and sera (enzyme-linked immunosorbent assay and Western blot) should be established when feasible.
2. WHO collaborating centers (Atlanta and Koltsovo) and other laboratories (e.g., Public Health Laboratory Service, London, United Kingdom; United States Army Research Institute for Infectious Diseases, Fort Detrick, Md.; National Institute for Infectious Diseases II, Tokyo, Japan; and WHO Collaborating Center for Diagnostics Development and the Armed Forces Institute of Microbiology, Munich, Germany) involved in orthopoxvirus research should continue developing and evalu-

ating rapid, sensitive, and specific virologic and serologic diagnostic tests suitable for use in-country, for both central laboratories and field use; these should include filter paper blood and salivary antibody and antigen assays. Collaborative efforts should focus on evaluating available reagents for incorporation into assays (e.g., monoclonal antibodies against orthopoxviruses, particularly monkeypox virus).

3. The WHO document on collection, storage and shipping of specimens from humans for monkeypox and hemorrhagic viruses should be updated. A technical note on monkeypox and varicella-zoster viruses (with clinical photographs) that includes an illustrated instruction card for field use is needed. Such a revision should conform to new WHO guidelines for specimen collection and transportation and be aimed at encouraging local workers to comply with these guidelines.
4. Support should be given to enhance education programs and training of personnel involved in field studies to obtain accurate case histories to accompany well-organized clinical sample sets.
5. WHO collaborating centers in poxvirus research (Atlanta and Koltsovo) and other laboratories involved in orthopoxvirus research (Munich, Fort Detrick, London, and Tokyo) should continue molecular biologic studies. This research should include DNA sequencing and virus structure, function, and biologic studies of new and earlier monkeypox virus isolates.
6. The capacity for performing epidemiological investigations, collaborative laboratory research, and training of staff at the WHO collaborating centers in Atlanta and Moscow should be increased, and other research institutes should be encouraged to bring more interested investigators into this research area.
7. Increased support should be obtained to undertake the required laboratory studies.

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Addendum. In May 2000, a report to ProMED, an Internet-based disease surveillance exchange, from the United Nations Office for Coordination of Humanitarian Assistance indicated that there were 315 deaths from monkeypox in Mbuji-Mayi, Kasai Oriental Province, DRC, in 1999. While the veracity of this report is in question, it underscores the importance of confirming such rumors and continuing effective surveillance for monkeypox, even in areas with difficult access. WHO is investigating this report.

Now that smallpox has been eradicated and vaccination has stopped, some have questioned whether monkeypox virus (like variola virus) could serve as an agent for biologic terrorism (9). Monkeypox appears to have a low attack rate for humans, to transmit with difficulty, and to be prevented by vaccination. While monkeypox does not seem to be a major peril as a biologic warfare agent, continued vigilance is indicated (28, 34).

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